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Real-life effectiveness of statins in the prevention of first acute coronary syndrome in France: A prospective observational study ☆

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ABSTRACT

Background: Evidence on the real effectiveness of statins on acute coronary syndrome (ACS) incidence is scarce. We assessed the effectiveness of real-life statins on the risk of first non-fatal ACS in a low-cardiovascular-risk country.

Methods: Systematic case–control study was conducted in 60 cardiology centres and 371 general practices from across France. A total of 2238 cases with first ACS within 1 month from recruitment and 2238 controls without history of ACS were included; controls were matched to ACS cases on sex, age, frequency of visits to GPs, date of recruitment and personal history of chronic diseases. Statin exposure and risk factors were documented through patient telephone interviews and validated against medical records. The index date was the date of ACS for cases. Adjusted odds ratios (OR) of first ACS and statin use were estimated by multiple conditional logistic regression models controlled for risk factors and propensity score for statin exposure.

Results: Statin use was associated with lower ACS risk, with an adjusted matched OR of 0.67; 95% confidence interval (CI): 0.56 to 0.79 for current use (within 2 months) and 0.73; 95% CI: 0.62 to 0.86 for any use within 24 months [atorvastatin: 0.83 (0.63–1.10), fluvastatin: 0.75 (0.43–1.30), pravastatin: 0.98 (0.72–1.34), rosuvastatin: 0.49 (0.35–0.68) and simvastatin: 0.62 (0.46–0.84)]. The preventive effect of statins on non-fatal ACS reached its maximum after one to four years of use.

Conclusion: A similar magnitude of effect for statin use was observed in real life, as compared to randomised clinical trials in France.

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1. Introduction

Lowering low-density lipoprotein (LDL) cholesterol to adequate targets is a major component of international guidelines for the primary and secondary prevention of ischaemic heart events. The role of statins is well established in the Cholesterol Treatment Trialists' Collaboration meta-analysis, including over 174,149 patients in 27 trials [1,2]. A meta-analysis restricted to participants without vascular disease suggested that reduction in LDL cholesterol decreases the risk of major cardiovascular events and death by 25% and 15%, respectively. Furthermore, risk reduction in non-fatal events showed a bimodal distribution being higher in patients with a low cardiovascular risk score (5-year risk at baseline <10%), opening the door for reconsideration of European guidelines for those individuals. Indeed, the usefulness of using statins for primary prevention in countries with low baseline risk of acute coronary syndrome (ACS) such as France has been challenged and caution has been urged in prescribing statins for primary prevention in low-risk patients [3].

Besides results from randomised trials (RCTs), little evidence is available on the real effectiveness of statins on MI incidence. Real-life impact can differ from RCTs on a number of factors including interaction between cardiovascular diseases and medications, distribution of risk factors in the population, physicians and patients' awareness of cardiovascular risks and prevention, physicians' prescribing habits and patients' adherence to statin prescriptions [4–8].

The aim of this study was to estimate the impact of statin utilisation on the risk of first non-fatal acute coronary syndrome in the general population of France, a country with a low incidence of coronary artery disease.

2. Methods

This study used two prospective registries of ACS and general practice patients systematically collected in France for pharmacoepidemiology general research (PGRx registries) between 2007 and 2011 [9,10]. ACS patients in these registries were patients presenting with a first recent (≤1 month) non-fatal ACS, recruited in a prospective and consecutive manner by participating cardiology centres. General practice registries included all consecutive patients visiting participating general practitioners (GPs) in the same areas as the cases during the same time period. Cases of ACS and controls with no history of ACS considered for inclusion in this study were those agreeing to participate, male and female, aged 18–79 years, living in France, and able to read and answer a telephone interview. Cases and controls were excluded if at least one of these items were present in their medical history: ACS, percutaneous coronary intervention, coronary artery bypass surgery or any other history of coronary artery disease, stroke or heart failure. The confirmation of ACS diagnosis in cases was provided by participating cardiologists based on the presence of at least two of the three following criteria: symptomatic criterion (characteristic pain), electrocardiographic criterion (ECG showing abnormality in at least two adjacent derivations), and biologic criterion (elevation of CPK-MB and/or troponin to twice the upper normal values). When the study started, this was called a myocardial infarction and therefore participating cardiologists were asked to recruit cases of first myocardial infarction. Recruiting centres were randomly audited for compliance with recruiting all consecutive eligible cases.

Statin exposure was documented as part of a systematic telephone survey of over 300 drugs through an interview method that has been previously validated against medical prescription or pharmacy records [11]. Interviews also included personal and medical history, socio-demographics and cardiovascular risk factors. Interviews of patients were conducted within 45 days of recruitment by trained interviewers. Statin exposure was classified as "current" if any statin was used in the 2 months preceding the index date (date of ACSin cases and date of recruitment in controls), or "recent" if any statin was used in the 24 months preceding the index date. Thus, patients who had stopped taking the drug for more than 24 months at inclusion were considered as not exposed. The main analysis considered exposure to any statin as a class versus no use of statin. Secondary analyses were conducted to quantify individual associations of statin molecules (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) with incidence of ACS versus no use of statin.

2.1. Statistical methods

Cases of ACS were compared to controls for their exposure to statins in a classic case–control analysis. Controls were randomly selected from the general practice registry and matched 1:1 to each case on sex, age (±5 years), number of visits to a GP in the year preceding the index date (0–1, 2–12, 13 + visits), date of consultation closest to the date of ACS for cases (±6 months if possible, otherwise ±1 year, ±2 years, or ±3 years), and personal history of non-cardiovascular (i.e., excluding diabetes, hypertension and obesity that were dealt with in the analyses) chronic disease (yes/no). Analyses were performed using multiple conditional logistic regression with case/control status as the dependent variable. Crude and adjusted odds ratio (OR) with 95% confidence interval (CI) are reported using the following variables for adjustment: smoking habits (current, former, never), body mass index (BMI, weight in kilograms divided by squared height in centimetres and categorised into: 19 or less, 20–24, 25–29, 30 or more), physical exercise (less than 30 minutes per day, 30 minutes or more per day), alcohol consumption (every day or several times a week, occasionally, never), occupation (unemployed, white-collar workers, blue-collar workers), and cardiovascular comorbidities (diabetes mellitus, hypertension, obesity).

Sensitivity analyses were carried out to assess interactions of various risk factors with statin use including age, sex, history of cardiovascular comorbidities (hypertension, diabetes and arterial disease other than coronary) and high vs. low dose of statin (high dose: >10 mg/day for atorvastatin, >40 mg/day for fluvastatin, >20 mg/day for pravastatin, >5 mg/day for rosuvastatin, >20 mg/day for simvastatin). The effect of self-reported adherence to the statin regimen was also examined (every day or several times a week vs. less frequent users). Odds ratios were compared between strata using Wald's test. A sensitivity analysis in the subgroup of patients, with at least one elevated cardiac-specific enzyme for myocardial infarction (troponin or CPKMB elevation exceeding twice the upper limit of normal), was performed to distinguish the risk in patients with atherothrombotic events. In addition, we checked the modification of statin's effect on the risk of acute coronary syndrome exercised by the variable Northern/Southern region. This has been tested by adding this variable in the model.

Finally, an analysis was conducted among controls that used statins to document a potential indication bias (i.e., whether there were differences in prescribing of statins based on differences in risk factors or not). We calculated a risk score based on all risk factors available, BMI, physical activity, smoking habits, alcohol consumption, hypertension, diabetes, hypercholesterolaemia, and geographical origin of patients. This partial risk score was used to stratify the relationship between statin utilisation and ACS in quartiles of risk, from low to high.

The statistical analysis was conducted using SAS software version 9.2 (SAS Institute, North Carolina, USA).

3. Results

Among centres participating in the PGRx registries, 60 cardiology centres and 371 GP settings participated in this study. The PGRx-ACS registry contained 2,908 cases, of which 2,238 met the inclusion criteria, could be reached for an interview and matched to controls for this study. The general practice registry for controls contained 9,294 patients, of which 2,238 were randomly selected to be matched to cases and met all the eligibility criteria. The final sample included 2,238 matched pairs for the analyses.

The majority of ACS cases were male (76%) with a mean age of 59.0 years which is consistent with the incidence of first lifetime ACS in the French population [12]. ST-segment elevation was present in 75.9% of the cases and elevated (> twice the upper limit of normal) cardiac-specific enzyme for myocardial infarction (troponin 1c, troponin T or CPKMB) in 88.5%. Detailed description of matched cases and controls according to main ACS risk factors is provided in Table 1.

After adjusting for risk factors, current use of any statin (used 2 months before the index date, regardless of use in the 3- to 24-month period) was associated with significant reduction in the occurrence of first non-fatal ACS by 33% (adjusted OR 0.67, 95% CI 0.56 to 0.79; $p < 0.0001$) (Table 2). Similarly, the use of any statin in the 24 months before the index date was associated with significant reduction in the occurrence of first ACS by 27% (adjusted OR 0.73, 95% CI 0.62 to 0.86; $p = 0.0002$).

We also repeated the main model in patients with at least one elevated cardiac-specific enzyme for myocardial infarction; and after adjusting for risk factors, current use of any statin was associated with an adjusted OR of 0.69, 95% CI 0.58 to 0.83. Similarly, in this same subgroup, the use of any statin in the 24 months before the index date was associated with an adjusted OR of 0.76, 95% CI 0.64 to 0.90.

In fact, further adjustments in the main model for patients' region (North vs. South) did not show any region-dependent effect (OR 1.02, 95% CI 0.90 to 1.16) and the OR associated with the use of any statin in the 24 months before the index date was very similar to the main result for the same time window (OR 0.73, 95% CI 0.62 to 0.86) when controlling for the region.